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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,233	04/10/2001	John A. Kink	OPHD-06331	8942

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EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	5

DATE MAILED: 09/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,233	KINK ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Objection

Claims 1-14 are objected to because of the following informalities: The preamble of claims 1 and 9 are ambiguous. It is not clear for what therapeutic indication is the method of treatment directed? Applicant is suggested to modify the language to recite " a method of treatment for necrotizing enterocolitis.". Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Eibl et al (N Engl J Med 1988;319:1-7) (Eibl I).

The instant claims are directed to methods of treatment comprising providing a human neonate a therapeutic formulation comprising antibody directed to Tumor Necrosis Factor (TNF) and administering said formulation to said neonate.

Eibl I administers oral immunoglobulin preparations to low-birth weight infants to inhibit the effects of anti-inflammatory mediators encompassing TNF in the infant's gut (see entire article, specially methods and discussion). Accordingly, the compositions of Eibl I comprise all elemental components of the

instant antibodies, therefore, Eibl's method inherently anticipates the limitations of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eibl et al US Patent 5,833,984 (Eibl II) or Lai US Patent 5,747,532 in view of Muguruma et al (Prenat Neonat Med 1998;3:571-579), Eibl I (Acta Pediat 83,666-668, 1994) and further in view of Emery et al US Patent 5,420,253.

Eibl discloses methods of preparing and using anti TNF-a IgA antibodies to reduce the inflammatory response at any site of interest (see abstract, col 4, lines 40-45; fig 3; example VI, col 11; claims 1-10). Eibl further teaches the corrolation between levels of TNF and the pathogenesis of neonatal necrotizing enterocolitis (see col 1, lines 60-66). Eibl fails to specifically use anti-TNF antibodies in treating NEC.

Lai discloses methods of treatment for inflammatory disease conditions that are caused by overproduction of nitric oxide comprising administering antibodies directed to pro-inflammatory factors such as TNF (see abstract, col 2, lines 35-55 lines; col 7, lines 1-5; example 4, col 14, line 67). Lai further teaches the use of his methods in treatment of ischemic, necrotizing and inflammatory enterocolitis encompassed by the term inflammatory bowel disease (e.g. ulcerative colitis or Crohn's disease)(see col 6 lines 37-67, examples 1-4, claims 1-2, 11, 19, 22, 31). Lai, however, does not disclose administration of anti-TNF antibodies to human neonates.

The role of TNF in the development of neonate necrotizing enterocolitis has been well established in the art. Accordingly, Wolf, Eibl I and Muguruma are merely used to set forth general knowledge in the art about TNF and NEC.

Wolf, for example, describes the general knowledge about the affects of oral IgA-IgG preparations in inhibiting TNF release thereby preventing the development of pathological changes associated with NEC in low-birth-weight infants (p. 667, 4th para).

Eibl I sets forth successful use of IgA-IgG in treating or preventing NEC among human infants (see abstract, discussion).

Muguruma also teaches the role of TNF in the pathogenesis of necrotizing enterocolitis (NEC) and ultimately the development of said condition specifically in low-birth-weight neonates (see abstract, entire document). Muguruma indicates the important role of pro-inflammatory agents such as TNF (page 575, 2nd, 3rd para-page 576, 2nd para.). Muguruma et al, however, fails to specifically teach the use of antibodies directed to PAF as a means of decreasing PAF activity among susceptible patients.

Finally, Emery is used to show that preparing avail antibodies are economicaaly teach methods of purifying high yield immunoglobulins from an avian source, wherein the antigen used may be a pro-inflammatory factor such as interlukins, prostoglandins, tumor necrosis factor and the like (see abstract, col 1 lines 1-21, col 2-3, col 4 lines 35-45, col 8 lines 38-67).

Eibl, Maguruma, Wolf, Lai and Emery teach methods of treating conditions that are caused by over expression of pro-inflammatory factors, therefore, their teachings are viewed as being in the same field of endeavor.

The role of TNF as a pro-inflammatory mediator in development of necrotic enterocolitis has been well established in the art as shown by Maguruma

and Wolf. Accordingly, even tough neither Eibl II nor Lai explicitly disclose the use of their antibodies in treating NEC in neonates, it would have been obvious to one of ordinary skill in the art at the time of invention to employ such products for treatment of NEC, because as suggested by Muguruma and Eibl I and Wolf, the ordinary skill in the art would have had a reasonable expectation of success in inhibiting the TNF activity among human infants, and thus, alleviating the pathological changes that lead to NEC.

Furthermore, Emery teach that immunoglobulin from an avian source such as chicken egg yolk can provide higher specificity and lower incidence of side effects at a lower cost, therefore, it would have been obvious to one ordinary skilled in the art to make anti-PAF antibodies from an avian source by the methods of Emery et al because such methods of preparing antibodies are conventional. One of ordinary skill in the art would have been motivated to combine said teachings because inhibiting the TNF inflammatory activity by anti-TNF antibodies would have provided beneficial effects to susceptible patients.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Russell Traverse can be reached on 703-308-

4603. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

ss
September 15, 2002

RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200